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Assessment of the nuclear medicine personnel occupational exposure to radioiodine

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ABSTRACT

Purpose: To physically and cytogenetically screen medical personnel of Department of Endocrinology and Nuclear Medicine, Holy Cross Cancer Center, Kielce, Poland (DENM) who are occupationally exposed to ^{131}I.
Materials and Methods: The exposure was monitored by whole-body and finger ring dosimeters. The thyroid iodine intake was measured by a whole-body spectrometer equipped with two semiconductor gamma radiation detectors. A cytokinesis-block micronucleus assay and the premature chromosome condensation technique were used to assess the aberration score. Cytogenetic analyses were carried out on a group of 29 workers and were compared to 32 controls (healthy donors), matched for gender and age.
Results: On average, the exposed group showed a significantly higher frequency of genetic damage and a higher proliferation index compared to the control group. Smoking status, age and duration of exposure influenced the observed effects in both groups. No differences in measured biomarkers were observed after stratification of the exposed group into two subgroups based on the measured ^{131}I activity below and above 6 Bq.
Conclusion: The findings suggest that radiation protection principles based on whole-body and finger ring dosimetry, supported by activity measurements with a whole-body spectrometer, may be insufficient to monitor the absorbed dose estimation of the nuclear medicine staff who are occupationally exposed to ^{131}I. Furthermore, their future health risks are influenced by confounders. Direct assessments comparing physical and biological dose estimations on the larger group are needed to accurately monitor occupational radiation exposure.

1. Introduction

Previous studies using a whole-body spectrometer at Institute of Nuclear Physics, Polish Academy of Sciences in Kraków (IFJ PAN) have shown that the medicine staff may have unavoidably absorbed different doses of iodine-131 (^{131}I, radioiodine) in the thyroid depending on their profession [1–6]. Iodine-131 is an important radioisotope that is selectively taken up by the thyroid gland and is popularly used in medical diagnostics and treatment procedures with a short radioactive half-life decay (T1/2 = 8.03 d) [3,4]. In the course of their duties, employees can be externally exposed to iodine when the source of radiation is the patient; radioactive iodine is typically taken in pill form (rarely as a solution) and is internally up taken by breathing air that is exhaled by patients treated with these radiopharmaceuticals [3]. Our previous studies have shown that exposure to radioiodine can lead to different extents of cellular DNA damage, not only in thyroid cells but also in other tissues (i.e., peripheral blood lymphocytes) [6]. In accordance with the Polish law, the exposure monitoring in nuclear medicine units is performed only with thermoluminescent dosimeters (TLDs) [1,4]. However, this type of monitoring does not provide any data on the

Abbreviations: BN, binucleated cells; CBMN, cytokinesis-block micronucleus test; DI, whole-body dosimeter; PHA, phytohaemagglutinin; HPBL, whole human peripheral blood lymphocytes; ^{131}I, iodine-131, radioiodine; ICRP, International Commission on Radiological Protection; MNi, micronuclei; NDI, nuclear division index; PCC, premature chromosome condensation technique; PI, finger ring dosimeter; TLD, thermoluminescent dosimeter

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doses incorporated into the thyroid gland or the total absorbed dose in the whole organism taking into account individual cell responses influenced by confounders [1,4,5].

In the light of previously published results [1,4,6], the aim of this study was to monitor the chromosomal damage and proliferation index in whole peripheral blood lymphocytes (HPBLs) of a group of medical staff exposed to ^{131}I by using a cytokinesis-block micronucleus test (CBMN) and the premature chromosome condensation technique (PCC) in comparison with results obtained by using a whole-body spectrometer and TLD measurements to assess the genotoxic potential of the exposure. We also investigated how other confounders such as age, duration of exposure and smoking status influenced the observed effects.

The frequency of micronuclei (MNi) and excess PCC fragments measured with the CBMN and PCC techniques are internationally accepted biomarkers of individual dose assessment in the field of biological dosimetry and radiation protection [7–11]. They are used to evaluate in vivo radiation exposure of occupational, medical and accidentally exposed individuals, usually in their HPBLs [7–11]. The advantage of these tests consists of providing simultaneous information on chromosomal damage and the rate of lymphocyte proliferation [7,8].

2. Materials and methods

2.1. Characteristics of study populations and blood collection

In the department where our study took place, ^{131}I is administered to patients to perform thyroid scintigraphy, treat hyperthyroidism and thyroid cancer treatment. The exposed group contained 29 employees (2 men and 27 women) of DENM. The men were 45 and 48 years old at the time of the measurement, whereas the women were aged 40–56 years (average age: 46.9 ± 4.5 years). The detailed characteristics of the exposed group is presented in Table 1 in the results section. The research was approved by the Bioethics Committee of the Regional Medical Board in Kraków (No. 111/KBL/OIL/2015). The same selection criteria were used for the control group. A total of 32 controls (1 male, 31 females; mean age 48.0 ± 8.6 years) were not exposed to radiopharmaceuticals and were recruited from internal medicine wards of the same hospital. Each participant in the study was asked to complete a survey questionnaire including personal data, gender and age, occupational activity (also in the past) and data on smoking habits, diet and previous exposure to radiation. Each of the examined subjects was informed about the scope and purpose of the investigation and gave their consent.

The peripheral blood samples from exposed and control subjects were collected in heparinized vacutainers by phlebotomy at the beginning of a working day at the end of 2017 (exposed group) and at the beginning of 2018 (control group). The samples were transported immediately to the laboratory of IFJ PAN within 2 h, at ambient temperature and were then immediately processed.

2.2. Cytokinesis-block micronucleus assay

The cytokinesis-block micronucleus assay was performed according to Fenech [8], as previously described [7].

All slides were coded and blinded to the scorer. The slides were analyzed for micronuclei frequency according to the criteria described by Fenech [8].

2.3. Premature chromosome condensation test

The cultures were treated similar to those used in the CBMN assay, following the IAEA guidelines and a previously published data [9,10]. Instead of cytochalasin-B, calyculin A (50 nM) was added to the culture medium exactly 30 min before ending the culturing process (48 h). Cell finding and image capturing were performed on a Metafer4 scanning

Table 1
Data of the exposed group, including age, profession, gender, duration of exposure, measured ^{131}I thyroid activity and doses [mSv] measured by whole-body dosimeter (DI) and finger ring dosimeter (PI) for 2016–2017.

Subject code	Age [y]	Profession	Gender	Duration of exposure [y]	^{131}I thyroid activity [Bq]	DI	PI	DI	PI
						2016		**2017**	
1	42	Cleaner	F	20	152 ± 40	< 0.40	–	< 0.40	–
2	47	Nurse	F	23	–	< 0.40	–	< 0.40	–
3	46	Medical doctor	F	21	< 5	< 0.40	–	< 0.40	–
4	48	Cleaner	F	20	91 ± 24	< 0.40	–	< 0.40	–
5	54	Nurse	F	33	< 5	< 0.40	–	< 0.40	–
6	51	Medical doctor	F	27	< 5	< 0.40	–	< 0.40	–
7	45	Nurse	F	21	< 5	< 0.40	–	< 0.40	–
8	52	Nurse	F	30	< 5	< 0.40	–	< 0.40	–
9	54	Technician	F	30	107 ± 28	0.72	3	0.77	1.77
10	48	Technician	M	22	217 ± 56	< 0.40	0.92	< 0.40	7.95
11	52	Nurse	F	30	< 5	2.31	–	< 0.40	–
12	43	Nurse	F	24	< 5	< 0.40	–	< 0.40	–
13	53	Medical doctor	F	30	< 5	< 0.40	–	< 0.40	–
14	45	Nurse	F	22	< 5	< 0.40	–	< 0.40	–
15	41	Nurse	F	20	66 ± 17	< 0.40	–	< 0.40	–
16	45	Nurse	F	22	38 ± 10	< 0.40	–	< 0.40	–
17	41	Medical doctor	F	15	–	< 0.40	–	< 0.40	–
18	41	Medical doctor	F	14	–	< 0.40	–	< 0.40	–
19	45	Medical doctor	M	20	–	< 0.40	–	< 0.40	–
20	41	Nurse	F	19	< 5	< 0.40	–	< 0.40	–
21	50	Nurse	F	26	< 5	< 0.40	–	< 0.40	–
22	47	Cleaner	F	25	–	–	–	–	–
23	56	Nurse	F	36	–	< 0.40	–	< 0.40	–
24	48	Nurse	F	25	< 6 ± 6	0.42	–	< 0.40	–
25	43	Cleaner	F	25	5 ± 2	–	–	–	–
26	49	Medical doctor	F	24	–	< 0.40	–	< 0.40	–
27	44	Nurse	F	20	16 ± 5	< 0.40	–	< 0.40	–
28	40	Nurse	F	14	< 5	< 0.40	–	< 0.40	–
29	49	Nurse	F	30	< 5	< 0.40	–	< 0.40	–

DI - whole-body dosimeter, PI - finger ring dosimeter, F- female, M- male.

Table 2
Comparative biomarker results of the exposed and control groups, stratified by smoking status.

Group	N	BNMN (mean ± S.D.)	MNi/1000BN cells (mean ± S.D.)	Number of BN cells with different number of MN (mean ± S.D.)				NDI (mean ± S.D.)	Excess PCC fragments (mean ± S.D.)
				+1	+2	+3			
Exposure									
Total	29	24.90 ± 11.56*	27.90 ± 13.29*	22.21 ± 10.19	2.38 ± 2.04**	0.31 ± 0.54***	3.04 ± 0.86***	0.43 ± 0.17**	
Non-smokers	18	26.61 ± 13.30	30.00 ± 15.44	23.56 ± 11.60	2.72 ± 2.32*	0.33 ± 0.59	3.00 ± 0.89***	0.41 ± 0.18**	
Smokers	11	22.09 ± 7.71	24.45 ± 8.25	20.00 ± 7.31	1.82 ± 1.40**	0.27 ± 0.47	2.36 ± 1.04**	0.47 ± 0.16	
Control									
Total	32	19.19 ± 6.14	20.31 ± 6.71	18.19 ± 5.95	0.97 ± 1.06	0.03 ± 0.18	1.71 ± 0.11	0.33 ± 0.14	
Non-smokers	17	18.94 ± 6.33	20.24 ± 6.97	17.59 ± 6.06	1.29 ± 1.16	0.06 ± 0.24	1.70 ± 0.12	0.28 ± 0.09	
Smokers	15	19.47 ± 6.13	20.40 ± 6.64	18.87 ± 5.95	0.60 ± 0.83	0.00 ± 0.00	1.71 ± 0.11	0.38 ± 0.17	

S.D. - standard deviation, BNMN - number of BN cells with MNi in 1000 binucleated cells, MNi/1000 BN cells - MNi frequency per 1000 binucleated cells, NDI - nuclear division index.

* Statistically significant difference ($p < 0.05$) vs. total control (Student's *t*-test).

** Statistically significant difference ($p < 0.05$) vs. total control (Mann-Whitney U test).

*** Statistically significant difference ($p < 0.0001$) vs. total control (Mann-Whitney U test).

system equipped with a Zeiss Axio Imager Z2 microscope (MetaSystems™, Altlussheim, Germany).

2.4. ^{131}I activity measurements

^{131}I thyroid activity measurements in the occupationally exposed group were performed with the whole-body spectrometer a few weeks prior to blood collection [1]. More detailed information concerning the methodology of the measurements and the dose assessments can be found in Brudecki at al. [1].

2.5. Whole-body dose estimation

Doses for 2016 and 2017 were measured using a whole-body dosimeter (DI) and a finger ring dosimeter (PI) provided by Laboratory of Individual and Environmental Dosimetry (LADIS) that were accredited to the EN-PN-ISO/IEC 17025 standard by Polish Centre for Accreditation. In all measurements, the individual TLDs were used to measure the operational value Hp(10) and Hp(0.07) [12].

2.6. Statistical analysis

The data were analyzed and presented graphically using Microsoft Office Excel 2013 and Statistica 13 (StatSoft, Tulsa, OK, USA). The various biomarkers were measured for each individual. The number of BNs (binucleated cells) with MNi and the MNi frequency were assessed based on the analysis of 1000 BN cells. To assess the lymphocyte proliferation rate, the nuclear division index (NDI) was calculated for the first 500 cells according to Fenech et al. [8]. The PCC fragments per cell in excess of 46 PCC chromosomes for each donor were scored in 100 G2/M PCC-phase cells [9,10].

The standard deviation (S.D.) was calculated for all measured biomarkers. Student's *t*-test and the Mann-Whitney rank–sum test for comparison of the biomarkers between the studied groups were used depending on the normality of the distributed biomarkers as verified by the Shapiro-Wilk test. P values of < 0.05 were considered to be significant and are indicated in the text. Linear regression analysis was used to assess the effects of confounding factors such as age and the duration of exposure on the induction of cytogenetic effects.

3. Results

Table 1 presents a summary for every subject in the exposed group as follows: age, profession, gender, years of exposure, measured ^{131}I thyroid activity and doses [mSv] by whole-body dosimeter (DI) and finger ring dosimeter (PI) for 2 years (2016–2017). For 13 subjects, the thyroid ^{131}I activity measured in 2016 was below the detection limit (DL < 5 Bq of ^{131}I), for another 7 we did not measure the activity. Among the remaining 9 individuals, the measured activities were found to vary between (5 ± 2) Bq and (217 ± 56) Bq for the cleaning staff members and nuclear technicians, respectively (Table 1).

Measurements were made via whole-body dosimeters (DI) for the years 2016 and 2017 and showed that 24 subjects had Hp(10) values lower than 0.4 mSv for 2016, and 26 subjects were below this level considering the 2017 year. For 3 workers (codes 9, 11, 24), higher Hp (10) values were observed in for 2016 (0.72, 2.31, 0.42), but they did not exceed the average annual dose limit (20 mSv/y). This dose limit was stipulated in the 2013/59 Euroatom (2014) directive [13], recommended by ICRP (International Commission on Radiological Protection) and acquired by the Polish law [1]. In the exposed group, for one donor only (code 9), the Hp(10) value was higher than 0.4 mSv but was lower than 0.78 for 2017. All presented values for DI and PI are subtracted from natural background. We did not receive whole-body dose estimation data based on DI and PI for two subjects. In the case of finger ring dosimeters (PI), values greater than 0.9 but less than 8.0 mSv were observed during 2016–2017 for two subjects (codes 9 and 10).

Cytogenetic monitoring was performed for all individuals who were previously monitored for thyroid activity. Table 2 presents the mean values of the measured biomarkers for both the exposure and control groups, stratified by smoking status.

Strong variation, indicated by high S.D. values between measured biomarkers, was observed for both groups (exposed and control). However, the mean value of cytogenetic damage, presented as the number of BNMNs, MNi frequency, number of BN cells with different numbers of MNi (2 and 3) and excess PCC fragments in the exposed group, was higher than in the control group (Table 2). Also, the nuclear division index was significantly higher in the exposed group compared to controls (Table 2). After the groups were stratified based on smoking status, we observed statistically significant differences between the exposed and control subjects only in the proliferation index and in the binucleated cells carrying 2 micronuclei. A higher frequency of excess PCC fragments in the exposure vs. control group ($p < 0.05$) was observed only among non-smokers.

We investigated the possible influence of measured I^{131} activity on cytogenetic endpoints, assessed with the CBMN and PCC techniques. Subjects from the exposed group were stratified into two subgroups according to the measured ^{131}I thyroid activity: Bq > 6 (7 donors, average activity 98.14 ± 17.71) and Bq < 6 or those without measurements (22 subjects). There were no differences among all of the measured biomarkers between these two subgroups. Surprisingly, we observed higher values of BMMN, MNi/1000, and BN with +1

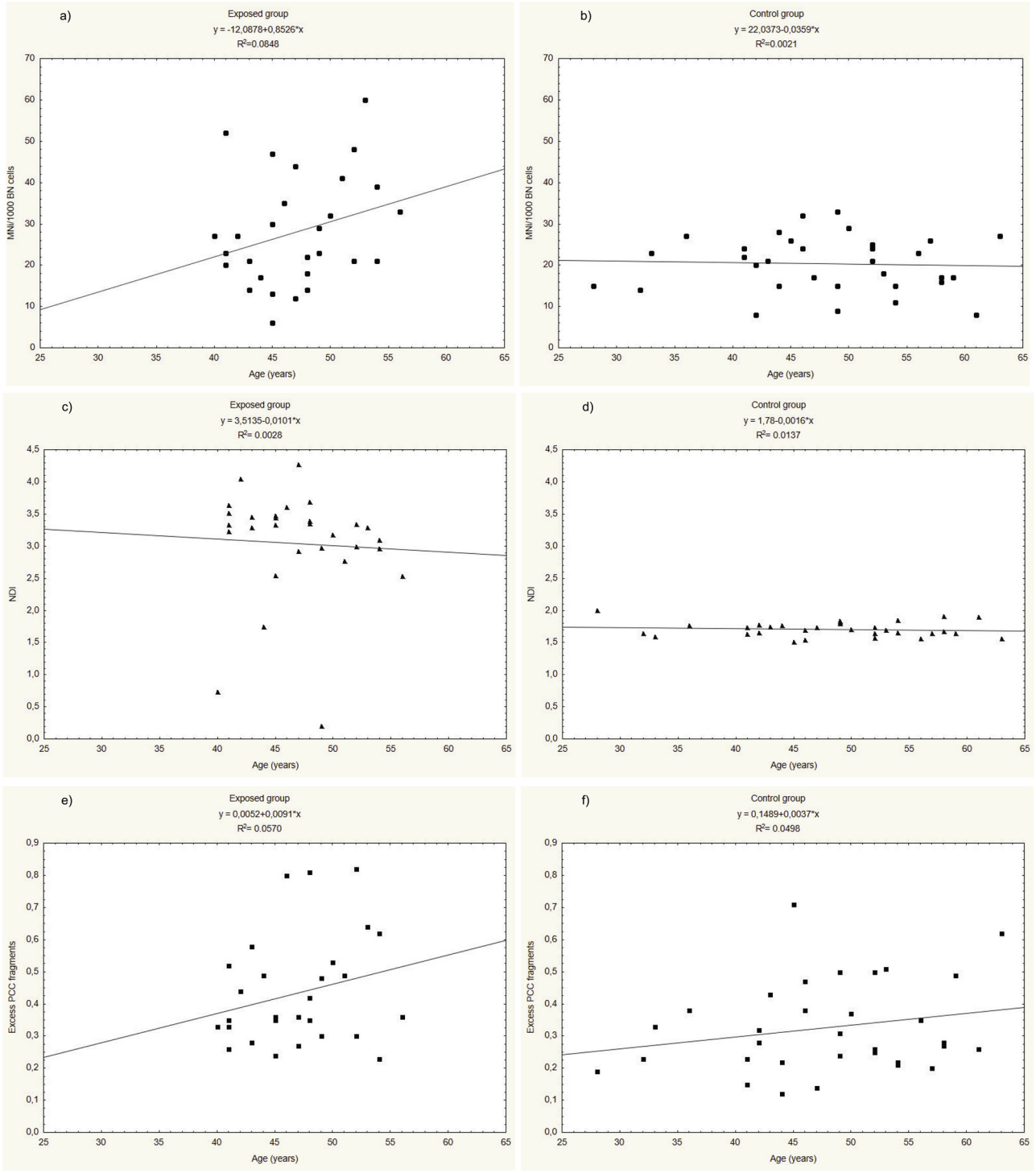

Fig. 1. Relationship between MNi frequency (Fig. 1a and b), excess PCC fragments (Fig. 1c and d), NDI (Fig. 1e and f) and age (years) of exposed and control subjects.

(25.91 ± 12.36 vs. 21.71 ± 8.58; 28.95 ± 14.13 vs. 24.57 ± 10.41; and 23.18 ± 11.01 vs. 20.00 ± 7.31, respectively) in the group with less activity/not measured vs. activity > 6 Bq. Furthermore, for two exposed subjects (codes 9 and 10) with a relatively high value of ^{131}I activity, which was also monitored by finger ring dosimeters, we did not observe higher values for the measured biomarkers than in others from the exposed group. By applying linear regression analysis, a positive correlation was noticed between the age and duration of exposure and the total number of MNi/1000 and PCC frequency in the exposed group (Figs. 1a, c, Fig. 2a and c). In the control group, with increasing age and exposure duration, a slight decrease of MNi was observed (Figs. 1b and 2b), while excess PCC increased (Figs. 1d and 2d). Our results also indicated an effect of age and exposure duration on the nuclear division index for both of the studied groups. As can be observed in Fig. 1e-f and Fig. 2e-f, there was a decrease in proliferation ability, with similar slopes but the NDI was higher in the exposed group than in the controls.

4. Discussion

In this study, we cytogenetically and physically monitored a group of medical staff exposed to ^{131}I to assess the genotoxic potential of

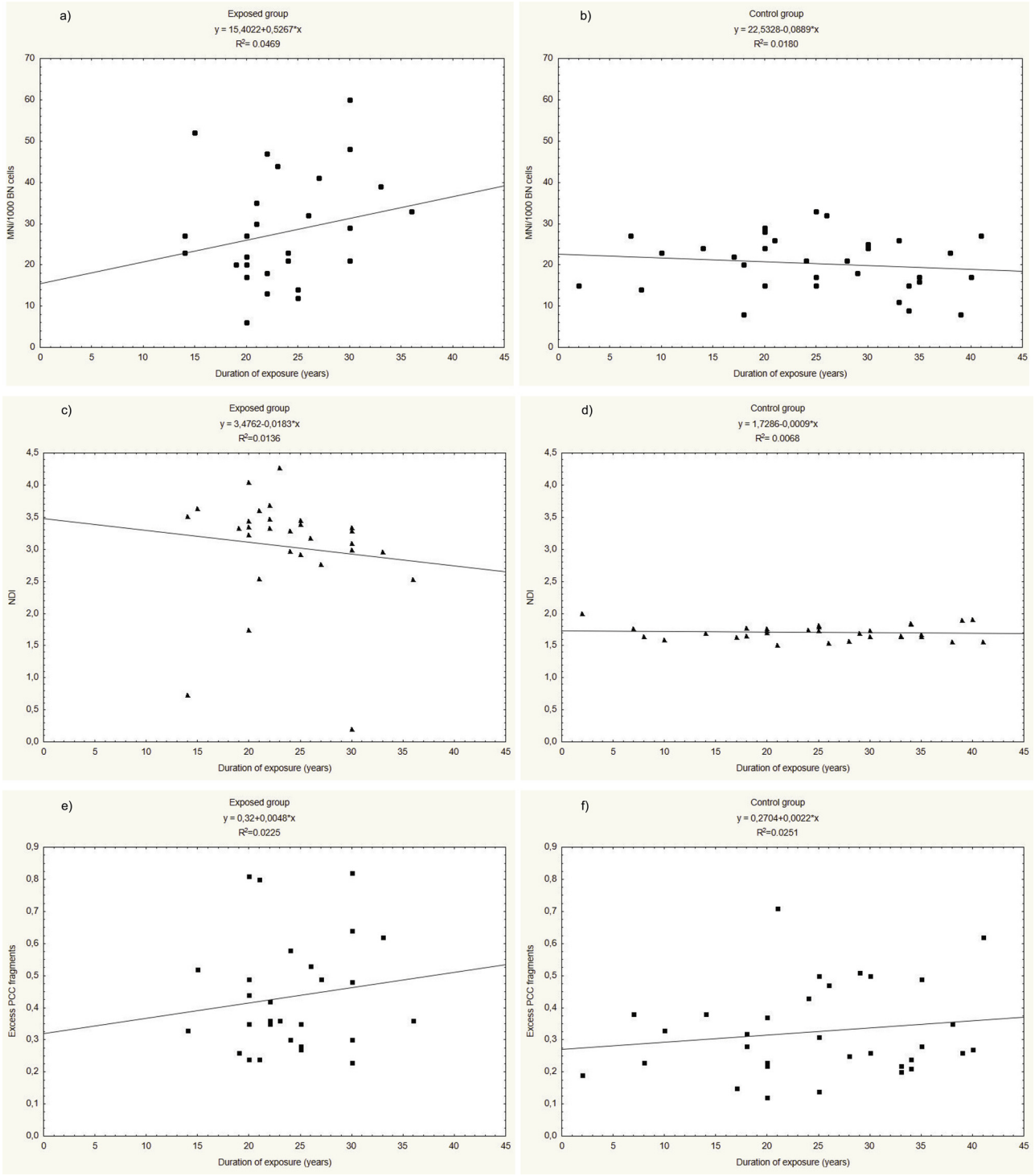

Fig. 2. Correlation between duration of exposure to ^{131}I and genotoxic effects (MNi/1000 BN cells, excess PCC fragments and NDI) assessed by linear regression analysis in the exposed and control groups.

exposure. We investigated how confounders such as age, duration of exposure and smoking status may have influenced the observed effects.

Notably, there is a baseline of spontaneous cytogenetic damage in individuals who were never exposed to radiation. The background of micronucleus frequencies found in our control subjects is in agreement with that reported in the literature [7,14]. As a new concept in the radiation biodosimetry field, in the present study an attempt was made to estimate the mean value of excess PCC fragments in the control group using a chemically induced PCC assay. Generally, most of the relevant studies have presented frequencies of acentric fragments or rings for one or a few donors (2–5) as a distribution for the dose-response curve construction [10,15]. The baseline mean value of NDI for the control group (1.71 ± 0.11) was in agreement with previously published data [10,16]. For the exposed group, the averaged mean was higher (3.04 ± 0.86), indicating that viable cells divided faster than in the control group and completed more than one nuclear division during the cytokinesis-block phase.

While confirming previous findings to some extent [1,9], the data we obtained show that the increased level of cytogenetic damage and the increased proliferation index in the group exposed to ^{131}I is still

highly significant for the donor for which we did not observe a higher level in the physical dosimetry assessment (Tables 1 and 2). This might indicate that the observed average higher values for the cytogenetic endpoints in the exposed group result from the accumulation of DNA damage induced by several factors, and it may not be possible to separate the impact of ^{131}I on the measured values. This suggests that physical dosimetry measurements alone might be insufficient in reflecting the occupationally received exposure, even if the reported physical values show the whole radiation exposure (monitored in people exposed to radioiodine at the workplace wearing TLDs all the time). It may also be caused by the limitations of the epidemiologic questionnaires that were used, which may bias the reporting values. Although the subjects responded to the paper questionnaires during a face-to-face interview, some may conceal information regarding their exposure in other workplaces or the total duration of exposure. In addition, nuclear medicine staff might be exposed to other nuclides (e.g., Tc-99 m, F-18, In-111, I-123, Y-90 and P-32) when performing diagnostic and therapeutic procedures.

Importantly, physical dosimetry is routinely used over many years for monitoring the levels of exposure received by radiation workers [3], but only biological monitoring provides information about the total, cumulative dose absorbed during the most recent few years, which can contribute to a more accurate occupational risk assessment at the individual or group level [6,18]. We are also aware that the biological techniques applied in this study have some disadvantages and limitations. One is the lower limit for dose detection of the CBMN assay and PCC technique that is employed in many laboratories, which is restricted to 0.2–0.5 Gy [9]. To assess the possible overexposure of occupationally exposed persons using cytogenetic markers appears to be challenging, because a large number of cells would have to be analyzed to obtain statistically relevant differences between exposed and control groups. Furthermore, the radioactive material is heterogeneously distributed in the body [9]. Direct comparisons of spectrometer results and physical dosimetry with cytogenetics might be a new route for epidemiological studies regarding radiation protection principles, but here we were not able to show a direct dose-effect relationship for those exposed to different amounts of ^{131}I. The main reason for this was a lack of ^{131}I thyroid activity data or values that were below the detection limit for more than half of the group (see Table 1). We consider this a limitation of this study; however, we believe that this attempt provides insights for additional and larger studies. To the best of our knowledge, this research is the first study that has simultaneously measured both external and internal exposure together with estimating the absorbed doses by cytogenetic monitoring in the same cases. Individual studies have been conducted that primarily employed the external monitoring of ^{131}I by different types of dosimeters [19] or internal measurements [4,5], as well as biological monitoring alone [9,19]. Based on detection limit criteria, we assessed the possible influence of the measured I^{131} activity on cytogenetic endpoints by stratifying the exposed group by the measured ^{131}I thyroid activity into greater or less than 6 Bq. We observed higher values of BMMN, MNi/1000 and BN cells with +1 in the group with less activity/not measured vs. activity > 6 Bq. This finding indicates that this group of workers shows an impact in the higher values of the cytogenetic biomarkers, and were unable to find the reason behind it. Therefore, this should be taken into consideration in any future studies.

The high variability between individuals found in our study (as shown by the value of ± S.D.) implies the necessity for biological monitoring. In this respect, it might be argued that the measured doses and ^{131}I activities seem to be in accordance with the law and are too low to have an impact on the health risk [3]. On the other hand, it is known that the major health risks associated with exposure to iodine-131 involve the thyroid gland, which concentrates this radionuclide [20]. Another limitation of this study is that it was difficult to establish an *in-vitro* dose-effect relationship between chromosome damage and exposure to low levels of ionizing radiation [9,21] that can be used to evaluate partial or the whole-body exposure. Any relationship should take into consideration the differences in background MNi frequency, the response variation of individual subjects and other biological variations such as biokinetic parameters that describe isotope intake, uptake and excretion [1,4,21,22].

The observed results could have arisen due to confounding factors affecting MNi frequency levels in humans, such as smoking, diet or environmental exposures [4,13,16,17]. Although we did not stratify subgroups according to the daily consumption of cigarettes, as has been done by others [23], our observations are supported by these findings, suggesting that smoking can affect the level of genetic damage induced in humans by ionizing radiation. Surprisingly, the frequency of MNi in the exposed group is higher for non-smokers than for smokers. Many authors have studied the genotoxic effects of tobacco using the micronucleus assay [9,19,24], but this has shown conflicting data, where smoking has either influenced or not influenced the lymphocyte response that was measured as a cytogenetic endpoint.

Many authors have reported that cytogenetic damage is a very good indicator of age and duration of exposure [14,25]. These factors may increase the incidence of genetic damage by an age-related number of unrepaired DNA strand breaks induced by endogenous or/and exogenous factors [24]. Our findings are consistent with other studies that have performed correlation analysis [6,26], which is a useful statistical tool in researching the influence of both factors on the incidence of cytogenetic endpoints. Notably, all relationships presented here represent visible tendencies; however, differences are not significant, probably due to the high variability between individuals and relatively small sample groups.

The results and discussion presented here are not sufficient for making strong recommendations, but rather may stimulate further investigations concerning protective measures in the case of individuals who have been occupationally exposed to ^{131}I. Our findings support the conclusions previously put forward by Brudecki et al. [1,4] who indicated that risk evaluation associated with chronic exposure ^{131}I must be systematic, controlled by physical dosimetry and should be estimated periodically as an integrated radiological protection standard of nuclear medicine personnel occupationally exposed to ^{131}I.

5. Conclusion

In this study, cytogenetic monitoring together with whole-body dosimetry and ^{131}I activity measurements were studied in HPBLs of nuclear medicine staff and compared to a control group. A strong variation between measured biomarkers of the exposed group was observed. The increased chromosome fragments and micronuclei frequencies found in workers indicate potential genetic hazards. Unfortunately, very little information is available regarding the adverse human health effects of ^{131}I exposure. These observations, confirmed by previous findings and suggestions, indicate the need for further studies with a greater number of exposed individuals, along with in vitro studies for estimating the impact of ^{131}I exposure on the observed higher frequency of cytogenetic damage.

Author contributions

Kamil Brudecki together with Justyna Miszczyk conceived an idea and collaborative project, Justyna Miszczyk and Agnieszka Panek carried out the experiments and measurements, Justyna Miszczyk and Kamila Rawojć wrote the manuscript as well as the statistics, tables and figures. Aleksander Gałaś provided a survey questionnaire and consent. Aldona Kowalska and Artur Szczodry selected exposed and control groups, conceived also an idea with Kamil Brudecki and Justyna Miszczyk. All authors have given approval to the final version of the manuscript.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent. Prior to blood collection, informed consent was obtained from the donors.

Human and animal rights

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Prior to blood collection, informed consent was obtained from the donors. The research was approved by the Bioethics Committee at the Regional Medical Board in Kraków (No. 111/KBL/OIL/2015). This article does not contain any studies with animals performed by any of the authors.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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